Pretreatment with a very low dose of intravenous esmolol reduces propofol injection pain

Çok düşük doz intravenöz esmolol ile öntedavi propofol enjeksiyon ağrısını azaltır

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Summary

Objectives: Propofol causes considerable pain upon injection, although different methods and propofol formulations have been used to decrease this pain. We aimed to investigate the effect of i.v. esmolol pretreatment on propofol injection pain.

Methods: Ninety ASA I-II patients undergoing elective surgery under general anesthesia were randomly assigned into three groups of thirty each. A 20 G cannula was inserted into the dorsum of the nondependent hand. After venous occlusion for one minute, groups E, L and S were pretreated with 5 mg/ml (total 2 ml) esmolol, 40 mg lidocaine and 2 ml saline i.v. respectively. After release of venous occlusion, one fourth of the total propofol dose was administered at a rate of 0.5 ml/sec. During the injection of both pretreatment solution and propofol, patient pain was assessed by using 4 point scale. Heart rate and non-invasive arterial blood pressure values were recorded before induction, just after entubation and five minutes after entubation.

Results: Demographic values were similar among groups. Incidence of pain on injection of propofol in the control, esmolol and lidocaine groups was 90%, 33.3%, 50% respectively ($p<0.05$). Heart rate, systolic arterial pressure, and diastolic arterial pressure values were not different between the groups.

Conclusion: Pretreatment with low dose esmolol i.v. seems to be effective in attenuating pain during propofol injection.

Key words: Anesthesia induction; esmolol; pain; propofol.

Özet

Amaç: *Propofol enjeksiyon ağrısını azaltmak için farklı yöntemler ve propofol formülleri kullanılsa da, propofol enjeksiyonu hatırı sayılır oranda ağrılıdır. Biz intravenöz esmolol öntedavisinin propofol enjeksiyon ağrısı üzerindeki etkisini incelemeyi amaçladık.*

Gereç ve Yöntem: *Genel anestezi altında elektif cerrahiye giden 90 ASA I-II grubu hasta randomize olarak 3 gruba ayrıldı. 20 G intravenöz kanül hastanın bağımsız elinin dorsaline yerleştirildi. Bir dakika venöz oklüzyondan sonra E, L ve S gruplarına sırasıyla 5 mg/ml (total 2 ml) esmolol, 40 mg lidokain ve 2 ml salin i.v. verildi. Venöz oklüzyon açıldıktan sonra total propofol dozunun dörtte biri 0.5 ml/sn hızında uygulandı. Öntedavi ve propofolün enjeksiyonu sırasında hastanın ağrısı 4 noktalı skala ile değerlendirildi. Kalp atımı, sistolik arteriyel ve diyastolik arteriyel kan basıncı değerleri indüksiyondan önce, entübasyondan hemen sonra ve entübasyondan 5 dakika sonra kaydedildi.*

Bulgular: *Demografik veriler gruplar arasında benzerdi. Propofol enjeksiyon ağrısının insidansı kontrol, esmolol ve lidokain gruplarında sırasıyla %90, %33.3 ve %50 idi ($p<0.05$). Kalp atım hızı, sistolik arteriyel kan basıncı ve diyastolik arteriyel kan basıncı değerleri gruplar arasında farklı değildi.*

Sonuç: *Düşük doz intravenöz esmolol ile öntedavi propofol enjeksiyon ağrısının azaltılmasında etkili görünmektedir.*

Anahtar sözcükler: Anestezi indüksiyonu; esmolol; ağrı; propofol.

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Submitted (*Başvuru tarihi)* 20.10.2011 Accepted after revision (*Düzeltme sonrası kabul tarihi)* 05.06.2012

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Introduction

Propofol provides good quality of anesthesia and rapid recovery. Hovewer, it often has the disadvantage of causing pain or discomfort on injection in 28%-90% of patients.[1] Several methods have been tried to reduce the pain associated with intravenous injection of propofol. These include the addition of lidocaine, cooling or warming the drug, diluting the propofol solution, injection of propofol into a large vein, previous injection of ondansetron, granisetron, metoclopromide, magnesium, thiopental with or without tourniquet.[1-7]

Esmolol is an ultra short acting, cardioselective beta-1 adrenergic receptor antagonist.[8] It is effective in preventing adrenergic responses to several perioperative stimuli, including laryngoscopy, endotracheal intubation with tracheal intubation, intraoperative events and tracheal extubation.[8-10] Esmolol has peripheral analgesic and cardiovascular properties. It is thought to be involved in pain modulation.[11,12]

In this study, our aim was to investigate the effect of esmolol pretreatment on propofol injection pain and to compare its effect with lidocaine.

Materials and Methods

After ethical approval for this study was provided by the ethical commitee of university hospital, written informed consent was obtained from all patients. Exclusion criteria included obesity (body mass index >30 kg/m^2), pregnancy, risk of aspiration of gastric contents, suspected or known difficult airway, presence of severe neurologic deficits or psychiatric disorders, use of medications likely to affect central nervous system, use of non-steroidal antiinflamatory drugs and opioids, significant cardiac and liver dysfunction, hypersensitivity to study drugs. No patients received analgesics during 24 hour preceding the surgery. ASA I or II aged 18-60 year, undergoing elective surgical procedures, lasting 1-3 hours, under general anesthesia were enrolled into the study.

None of the patients were premedicated before entering the operating room. After instituting electrocardiogram, noninvasive arterial blood pressure, and pulse oximetry monitoring a dedicated 20 gauge cannula was inserted into the dorsum of the non-dependent hand for administration of study drugs With the help of a computer generated table of random numbers patients were assigned into one of 3 groups of 30 each.

The running carrier fluid was not begun before any study drug administration. All pretreatment drugs were prepared in 2 ml and coded by an anesthesiologist who was not involved directly in the study. All study drugs were maintained at room temperature and used within 30 min of preparation. A rubber tourniquet was placed over upper arm to produce venous occlusion for sixty seconds. All patients were pretreated with one of the pretreatment solutions; Group E: 10 mg esmolol diluted to 2 ml, (Brevibloc Premix 10mg/ml Baxter, Eczacıbaşı), Group L: 40 mg lidocaine, Group S: 2 ml NaCl 0.9% solution at a rate of 0.5 ml/sec. We asked the patients if they felt any pain during administration of pretreatment solution. The induction dose of propofol was 2.5 mg/kg. One minute after the injection of the pretreatment solutions , the tourniquet was released and one fourth of total calculated dose of propofol (Diprivan 1% Zeneca Ltd, Macclesfield, Cheshire, UK) was injected at a rate 0.5 ml/sec.

Before the administration of propofol, the patient was requested to rate immediately any sensation of pain during injection. A blinded anesthesiologist asked the patient to evaluate the pain score of propofol injection.

Pain was graded using a four point scale published by McCrick and Hunter.[4] 0=no pain, 1=mild pain (pain reported in response to questioning without any behavioural sign), 2=moderate pain (pain reported in response to questionning and accompanied by a behavioural sign or pain reported spontaneously without questionning) and 3= severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears).[4]

After the remainning dose of propofol was injected, fentanyl 1 mcg/kg, vecuronium 0.1 mg/kg was administered to fascilitate endotracheal intubation. Two minutes after vecuronium injection, trachea was intubated and anesthesia was maintained with isoflurane 1-2 vol % and N_2O 50% in O_2. Noninvasive arteriel blood pressure and heart rate were

Table 1. Demographical data

Group	Esmolol	Lidocaine	Normal saline
Age (years)	39.1±13.7	41.8±11.8	40.2±2.8
Height (cm)	168.1±6.5	168.7±6.7	167.5±8.5
Weight (kg)	68.6±15.1	74.7±15.0	71.9±15.8
BMI (kg.m-2)	24.2±4.7	26.4±6.0	25.6±5.2
Gender (Male/Female)	11/19	12/18	12/18
ASA (I/II)	23/7	23/7	21/9

Data is given as Mean±SD or number of patients, p>0.05.

recorded before induction (T1), just after intubation (T2) and 5 minutes after intubation (T3). Any complications such as pain, edema, wheal or flare response at the injection site was questioned 24 hour after operation.

Statistical analysis

Data analysis was performed by using Statistical Package for Social Sciences (SPSS) version 11.5 software (SPSS Inc., Chicago, IL, United States). Shapiro-Wilk test was used to test the normality of distribution for continuous variables. Data were expressed as mean ± standard deviation for continuous data, number of cases and percentages were used for categorical data. While, the mean differences among groups were compared by One-Way ANOVA, otherwise, Pearson's Chi-square test was used for the comparisons of the proportions. Repeated Measures of ANOVA was applied for evaluation of hemodynamic parameters. When the p-value from the variance analyses are statistically significant to know which time differs from which others, Bonferroni Adjusted multiple comparison test was used. A *p* value less than 0.05 was considered statistically significant. The Bonferroni Adjustment was applied for all possible multiple comparisons controlling Type I error. Assuming that the incidence of pain after propofol i.v. is 70% and that this would be reduced to half after pretreatment, power analysis with alpha error of 0.05 and a beta error of 0.2 showed that 30 patients in each group were required.

Assuming a mean pain score of 1.5 with a standart deviation of 1.27 patients each in three equal groups would be enough to reveal a 50% decrease in pain scores with the same alpha and beta errors. This study consisted of 90 consecutive patients.

Results

There were no statistically significant differences among groups regarding demographic data (Table 1). Pain after pretreatment drugs were not different among groups (Table 2). Pain scores demonstrated an increase within time. The incidence of pain at propofol injection was less in the two study groups when compared to saline group (Table 2) (p<0.05). The incidence of pain was not statistically different between esmolol and lidocaine groups (Table 2). The number of patients with pain during injection of propofol are listed in (Table 3). SAP, DAP, MAP and HR values were not different between the groups at T1, T2, T3 times (Table 4). No complication such as pain, edema, wheal or flare response were observed at the injection site within the first 24 hour after the operation.

Table 2. Incidence of pain

Group	Esmolol	Lidocaine	Normal saline
After pretreatment	–	–	–
During injection	10 (33.3%)*	15 (50.0%)*	27 (90.0%)

Number of patients with pain (Incidence %)
*p<0.05 compared to normal saline group.

Table 3. Number of patients with pain during injection of propofol in the study groups

Group	Esmolol	Lidocaine	Normal saline
No pain	20	15	3
Mild pain (A)	10	9	7
Moderate pain (B)	0	6	13
Severe pain (C)	0	0	7
Pain (A+B+C)	10	15	27

Discussion

In this study, we found that esmolol at this low dose attenuated propofol injection pain as effective as lidocaine. The incidence of pain during propofol injection in the control group was 90% compared with 33.3% in esmolol and with 50% in lidocaine group.

Among 33 anesthesia outcomes, propofol induced pain ranked seventh when both clinical importance and severity were considered.[13] Minimizing propofol injection pain is an important clinical goal, because it may influence the patient's perception of quality and acceptibility of anesthesia.

Several methods have been used to reduce the incidence and severity of propofol injection pain. Cooling of propofol, NSAID's, ephedrine pretreatments,

Table 4. Hemodynamic data

Variables	Esmolol	Lidocaine	Normal saline
Systolic blood pressure (mmHg)			
T1	137.5±17.34†	138.0±16.76†	139.2±18.69†
T2	98.6±12.83†‡	104.0±17.19†‡	110.5±17.29†‡
T3	127.6±23.41‡	133.9±23.59‡	129.1±14.49‡
Diastolic blood pressure (mmHg)			
T1	81.0±8.92†	81.1±11.09†	81.4±10.31†
T2	60.9±11.28†‡	62.4±15.28†‡	66.3±14.12†‡
T3	81.5±15.86‡	84.9±13.63‡	81.7±12.78‡
Mean blood pressure (mmHg)			
T1	101.5±13.23†	101.6±14.92†	102.6±13.89†
T2	72.2±11.37†‡	77.5±15.49†‡	80.4±13.83†‡
T3	98.0±18.67‡	99.6±24.78‡	99.6±13.45‡
Heart rate (beats per minute)			
T1	85.8±11.13†	83.2±15.67	84.9±16.92
T2	76.7±10.63†‡	78.4±14.91‡	78.3±10.74
T3	87.0±14.16‡	87.2±15.23‡	85.8±11.80
Saturation (%)			
T1	98.6±1.50¶	98.3±1.86¶	98.0±1.69†¶
T2	99.3±0.92	99.4±0.90	99.4±0.85†
T3	99.1±0.76¶	98.9±1.14¶	99.1±0.90¶

Data is given as Mean±SD, there is no statistically significant difference among groups according to the Bonferroni Correction (p>0.017).
†p<0.001 compared to T1 and T2 measurements.
‡p<0.001 compared to T1 and T3 measurements.
¶p<0.01 compared to T2 and T3 measurements.

oral clonidine, changing propofol infusion rate were used with various success.[2,4,14-17] Hovewer, even in patients who received most popular lidocaine treatment, the incidence of pain has been reported as frequent as 32%-48%.[15]

Propofol is an excellent anesthetic that belongs to the group of phenols, which can irritate the skin, mucous membrane and venous intima. It may activate the kallikrein-kinin system and release bradykinin, thereby producing venous dilatation, and hyperpermeability, which increases the contact between the aquaeous phase of propofol and free nerve endings resulting pain on injection.[18] Pain on injection of propofol can be immediate or delayed. The immediate pain could be the result of a direct irritant effect, but the cause of delayed pain is the kinin cascade.[18]

Esmolol, which is primarily indicated in the treatment of hypertension and tachycardia during anesthesia, has been claimed also to modulate pain pathways.[19] Clinical evidence obtained during anesthesia supports this idea. Esmolol has similar properties to alfentanil as a supplement to propofol/N_2O anesthesia and esmolol has some anesthesia sparing effects, reducing the anesthetic requirements for skin incision during propofol/N_2O and morphine anesthesia in humans.[20]

Hovewer, direct role of esmolol in the modulation of pain pathways during anesthesia has been questioned. Davidson et al.[11] showed that esmolol has direct analgesic properties in rats following the injection of formalin. In this study, it was shown that esmolol is involved in the modulation of pain. Associated cardiovascular changes which have been shown to be independent of nociceptive behaviour directly related to the level of the pain stimuli.

The sympatic nervous system is involved in pain via the potentiation of mediators such as IL -8 and increased sensitization to substance P.[19] Other beta blockers were also shown to have analgesic properties. Cunha et al. reported that atenolol and propranolol inhibited IL-8 induced hyperalgesia.[19] Hagelüken et al.[21] emphasized that milimolar range concentrations of some beta blockers have local anesthetic like properties and can activate GTPase activity and inhibit the delivery of spinal pain signals. In animals, propranolol prolonged sodium- channel blocker (tetradoxin) induced sciatic nevre blockade significantly.[22] Inhibitory G protein coupled receptor agonists act on postsynaptic inhibition via G protein coupled potassium channels or via the presynaptic inhibition of neurotransmitter release.[22] Avram et al.[23] demonstrated that beta adrenergic receptor antagonists decreases hepatic blood flow, metabolism of opioids and reduces the need for postoperative use of analgesics.

Although i.v esmolol produces its analgesic and associated cardiovascular properties peripherally, central beta-1 receptor blockage may also be involved in attenuation of pain related to propofol injection.[19] Esmolol may block beta adrenoreceptors within the brainstem and decrease the neuronal inflow into central nervous system.[24]

The dose of esmolol was chosen arbitrarily, depending on a pilot study which shows that such a low dose used in our study may be effective to attenuate propofol injection related pain. There is a dose dependent risk of hypotension and bradycardia, when esmolol is combined with anesthetics such as propofol and fentanyl. But in our study, we did not observe such an event since the esmolol dose used in this study is too low to cause such an effect.

Premedication with an opioid or sedative may reduce the incidence of injection pain. Therefore, to maintain the integrity of our results, no premedication was administered to any of the patients.

Duration of venous occlusion and the dose of lidocain used were based on meta-analysis which concluded the optimal method for prevention of propofol associated pain is to give lidocaine 0.5 mg/kg i.v while a tourniquet applied to the forearm for a period of 30-120 seconds before injection of propofol.[25]

In conclusion, pretreatment with esmolol 10 mg is as effective as 2% lidocaine (40 mg) 60 seconds prior to propofol in attenuating pain associated with propofol injection. Further studies are required to find out the exact mechanism of this effect. Dose response relationship should also be defined with further studies in order to optimize the effects of esmolol at anesthesia induction.

Administration of sufficient dose of esmolol may be a new treatment strategy for propofol injection pain with benefits of reducing anesthetic and opioid requirement, maintainning hemodynamic stability, and achieving early recovery from anesthesia.[26]

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